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Ipomoeassin F, a new cytotoxic macrocyclic glycoresin from the leaves of *Ipomoea squamosa* from the Suriname rainforest[†]

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Abstract

A new cytotoxic macrocyclic glycoresin, ipomoeassin F (**6**), has been isolated from the leaves of *Ipomoea squamosa*. The structure was elucidated by the interpretation of spectral data. Compound **6** was strongly active in the A2780 (human ovarian cancer cell line) assay with an IC_{50} value of 0.036 μM.

Keywords

ipomoeassin F; glycoresin; *Ipomoea squamosa*; Convolvulaceae; cytotoxicity

1. Introduction

We have previously reported the isolation of the five cytotoxic macrocyclic glycoresins ipomoeassins A-E (**1–5**) from the leaves of *Ipomoea squamosa* Choisy (Convolvulaceae) from the Suriname rainforest [2]. Subsequent to this work we re-examined a fraction from the final HPLC separation which had eluted just after ipomoeassin A (**1**). This fraction had originally been assumed to consist of ipomoeassin A, based on its ^{1}H NMR spectrum, which was very similar to that of **1**, and its R_f value on TLC (silica-gel, CH_2Cl_2:CH_3OH; 40:1), which was identical to that of **1**. Further chromatography of the fraction by HPLC (C8, 75% CH_3CN/H_2O) indicated however that the fraction contained a new compound (**6**), with a different retention time (t_R: 15.2 min) from that of compound **1** (t_R: 11.8 min).

2. Results and Discussion

Compound **6** was obtained as a colorless oil, and its HR FABMS gave a pseudomolecular ion $[M+1]^+$ at *m/z* 831.4211 (calcd for $C_{44}H_{63}O_{15}$ 831.4167), 28 amu more than that of ipomoeassin A (**1**). Its IR, UV, and ^{1}H NMR spectra were nearly identical to those of compound **1**. The major difference between their ^{13}C NMR spectra was located in the high field region (10 to 50 ppm), and it was thus deduced that compound **6** was a homolog of **1** with a C16 rather than a C14 hydroxyacid side chain, with two more methylenes than in **1**. The oxygenated

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methine must be located at position 11 since H-11 showed HMBC correlations to C-12 and C-13, and H_3-16 to C-14, and C-15. The chemical shifts of C-1 to C-6 were close to those of **1**, and the signals for C-7 to C-16 matched those of 11-hydroxyhexadecanoic acid [3], which confirmed the above deduction. The spin systems of **6** were determined from COSY and TOCSY spectra. The connectivities from H-1 of fucose to C-11, H-1 of glucose to C-2 of fucose, H_2-6 of glucose to C-1 of the side chain, H-4 of fucose to the acetyl carbonyl, and H-3 and H-4 of glucose to the tigloyl and *E*-cinnamoyl carbonyls, respectively, were established from HMQC and HMBC spectra. The configurations at position-11 and the sugar moieties were determined by analysis of its ROESY spectrum (Figure 1). Hence, the structure of **6** was determined as shown.

Compound **6** exhibited potent cytotoxic activity against A2780 human ovarian cancer cell lines with an IC_{50} value of 0.036 μM, which was much more active than compound **1** (0.5 μM) [1]. Here we can see again that sometimes a slight modification of the structure will enhance the activity dramatically.

3. Experimental

3.1 *General Procedures*

General experimental procedures, cytotoxicity bioassays, plant material, and isolation procedures were as previously described [2].

3.2 *Isolation*

The crude extract of E940631 (10 g, IC_{50}: 8.0 μg/mL) was separated into five fractions and fraction III was purified by HPLC over C18 using 75% MeCN/H_2O to yield ipomoeassins A-E (**1-5**) as described previously [2]. A fraction collected immediately after compound **1** was examined by ^{1}H NMR and normal phase TLC (silica-gel, CH_2Cl_2:CH_3OH; 40:1, R_f = 0.3), and appeared to be identical with or very similar to compound **1**. Further chromatography of this fraction was carried out using a semi-preparative C8 Varian Dynamax HPLC column (5 μ, 250×10 mm) with 75% CH_3CN/H_2O as eluents to afford compound **6** (1.4 mg, t_R: 15.2 min), which had a different retention time from that of compound **1** (t_R: 11.8 min).

3.3 Ipomoeassin F (6)

colorless oil; $[\alpha]_D^{22}$ -54° (*c* 0.16, EtOH); IR (film) ψ_{max} 3400, 2931, 2857, 1719, 1636, 1450, 1378, 1247, 1154, 1071, 1017; UV (EtOH) λ_{max} (log ε) 278 (4.18) nm; ^{1}H NMR (500 MHz, C_6D_6) and ^{13}C NMR (125 MHz, C_6D_6) data, see Table 1; HRESIMS *m/z* 831.4211 (calcd for $C_{44}H_{63}O_{15}$ 831.4167).

Acknowledgments

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Reference

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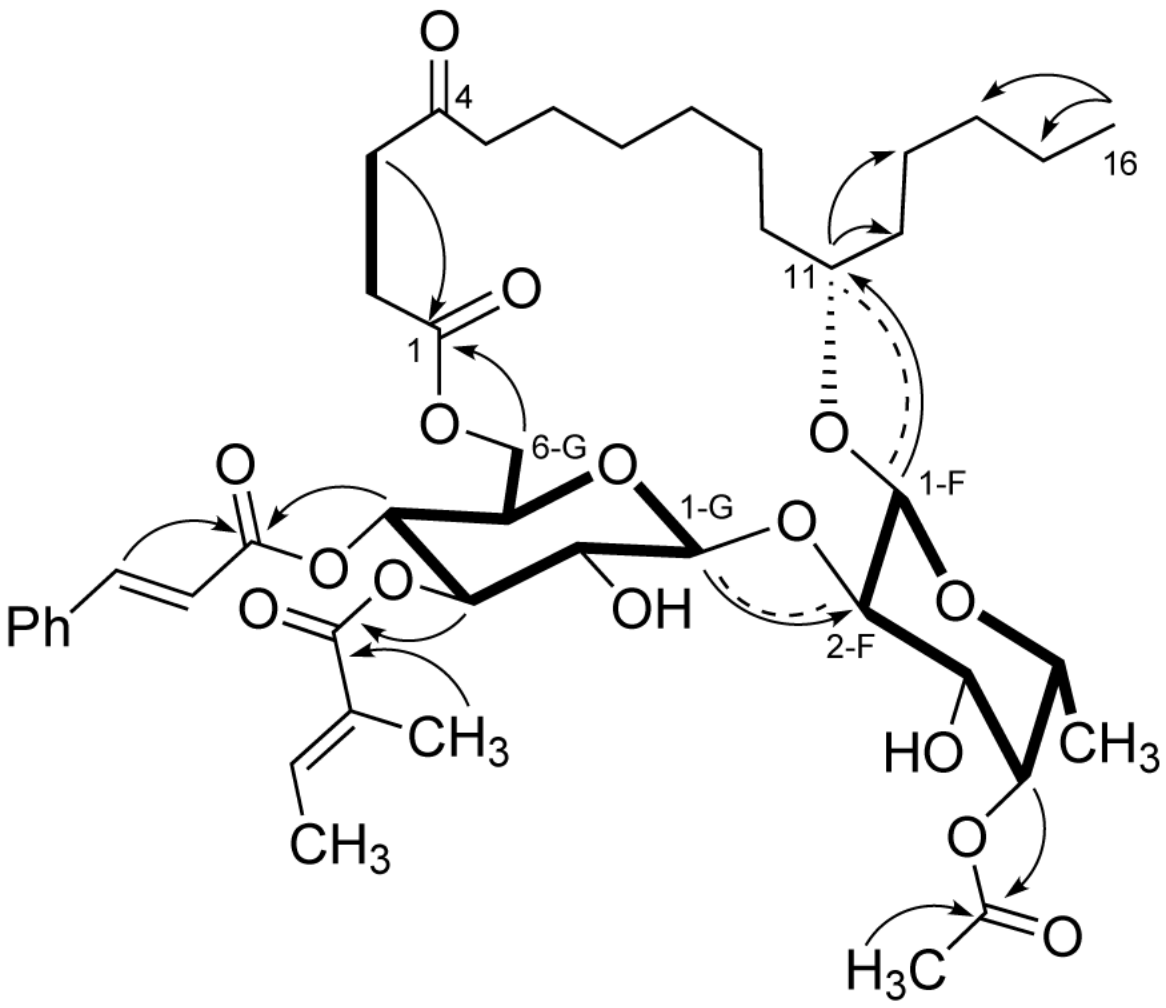
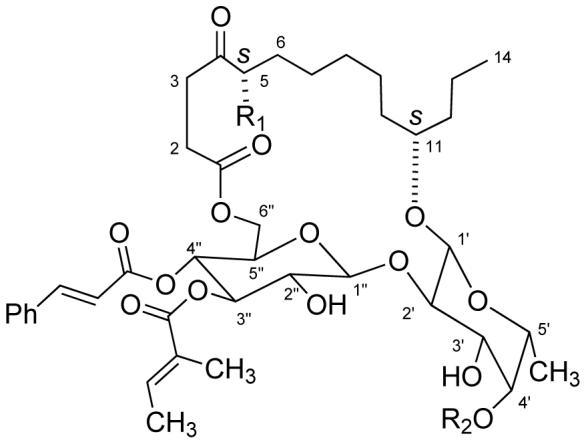
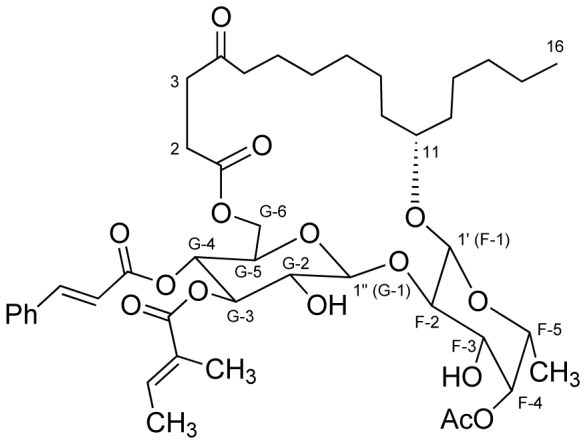


Figure 1.
Key HMBC (arrows), ROESY (dashed), COSY and TOCSY (bold) correlations of ipomoeassin F (**6**)



1 R_1 = H; R_2 = Ac
2 R_1 = R_2 = H
3 R_1 = OH; R_2 = Ac
4 R_1 = OAc; R_2 = Ac
5 R_1 = OAc; R_2 = H



6

Structures 1-6.

Table 1

^{1}H and ^{13}C NMR data of ipomoeassins F (**6**) and A (**1**)[a]

no	6	1	6	1
1			171.5	171.5
2	2.39 ddd (17.3, 9.6, 3.2) 2.14 ddd (17.3, 7.4, 3.4)	2.40 ddd (17.4, 9.4, 3.4) 2.14 ddd (17.4, 7.7, 3.5)	37.4[b]	37.3[b]
3	2.65 ddd (16.4, 7.4, 3.2) 2.52 ddd (16.4, 9.6, 3.4)	2.65 ddd (16.1, 7.7, 3.4) 2.52 ddd (16.1, 9.4, 3.5)	29.6[c]	29.7[c]
4			208.3	208.4
5	2.07 t (7.1)	2.07 t (6.0)	41.6	41.6
6			23.5	23.8
7			28.7	28.7
8			29.4[c]	29.4[c]
9			25.5	25.5
10			34.3	34.3
11	3.72[b] m	3.72[b] m	79.4	79.0
12			35.4[b]	37.6[b]
13			25.2	18.7
14		0.95 t (7.1)	32.3	14.4[d]
15			23.1	
16	0.92 t (7.1)		14.3[d]	
1′	4.40 d (7.6)	4.40 d (7.7)	100.8	100.8
2′	3.96[c] dd (9.4, 7.6)	3.96[c] dd (9.5, 7.7)	84.0	84.0
3′	3.72[b] dd (9.4, 3.7)	3.72[b] dd (9.5, 3.7)	72.8[e]	72.7[e]
4′	5.15 br d (3.7)	5.15 dd (3.7, 0.5)	72.8[e]	72.9[e]
5′	3.11 br q (6.4)	3.10 qd (6.4, 0.5)	69.0	69.0
6′	1.11 d (6.4)	1.10 d (6.4)	14.1[d]	14.1[d]
1″	4.54 d (7.8)	4.52 d (7.9)	106.5	106.6
2″	3.91[c] dd (9.8, 7.8)	3.91[c] dd (9.7, 7.9)	74.8	74.8
3″	5.40 t (9.8)	5.39 t (9.7)	76.7	76.4
4″	5.70 t (9.8)	5.69 t (9.7)	67.8	67.8
5″	3.27 br d (9.8)	3.24 ddd (9.7, 3.2, 1.6)	73.0[e]	73.0[e]
6″	4.67 dd (12.6, 3.0) 4.13 br d (12.6)	4.66 dd (12.6, 3.2) 4.11 dd (12.6, 1.6)	61.5	61.5
AA-1			170.9	171.0
AA-2	1.84 s	1.82 s	20.5	20.5
TA-1			168.7	168.5
TA-2			128.0	128.0
TA-3	6.95-7.00 m	6.95 m	139.4	139.2
TA-4	1.26 d (7.1)	1.23 d (7.1)	16.6	16.6
TA-5	1.71 br s	1.68 br s	12.0	12.1
CA-1			165.6	165.6
CA-2	6.39 d (16.0)	6.39 d (15.9)	117.6	117.6
CA-3	7.82 d (16.0)	7.81 d (15.9)	146.1	146.1
CA-4			134.4	134.5
CA-5	6.92 d (7.1)	6.89-7.07	128.5	128.5
CA-6	7.05 d (7.1)	6.89-7.07	128.9	128.9
CA-7	6.95-7.00 m	6.89-7.07	130.4	130.4

[a] δ (ppm), in benzene-d_6, 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR; multiplicities; *J* values (Hz) in parentheses. AA = acetoyl; TA = tigloyl; CA = cinnamoyl

b-e overlapped